

Attorney Docket No.: 045636-5054  
Application No.: Unassigned

Alzheimer's disease is a neurodegenerative disorder which affects from 1 to 6% of the population over the age of 65. One of its characteristics is the presence of senile plaques which contain  $\beta$ -amyloid ( $\beta$ A4 or BAP), which is a toxic product derived from APP and consisting of peptides of 39 to 42 amino acids, which are engendered by cleavage of APP by two proteases,  $\beta$ - and  $\gamma$ -secretase. Moreover, a third enzyme, named  $\alpha$ -secretase, cleaves APP between the  $\beta$ - and  $\gamma$ -sites, therefore making it impossible to form the supposedly pathogenic  $\beta$ A4. None of these secretases has, to date, been identified, even though there are legitimate suspicions regarding the PS1 protein (product of the Presenilin-1 gene, mutated in familial forms of Alzheimer's disease). In fact, PS1 may be either  $\gamma$ -secretase or one of its cofactors. Finally, other cleavage sites exist in the C-terminal domain, including the site for caspases (N. Barnes et al., J. Neuroscience, 1998, 18, 15, 5869-5880), between the aspartate and alanine residues of SEQ ID NO: 1 (positions 16 and 17). It remains that the mechanisms responsible for the toxicity of  $\beta$ A4 are unknown and that the relationship between the presence of  $\beta$ A4 in the plaques and the pathological condition has not been elucidated. It is probable that other factors and/or other domains of the molecule are also involved.

**IN THE CLAIMS:**

Please cancel claims 1-11 and add the following claims 12-20.

05-09-2001

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FR000217

NOVEL APPLICATIONS OF PEPTIDES DERIVED FROM THE  
CYTOPLASMIC DOMAIN OF AMYLOID PRECURSOR PROTEIN

5 The present invention relates to novel applications of  
peptides derived from the cytoplasmic domain of amyloid  
precursor protein. Amyloid precursor protein (APP), is  
a protein of unknown function, the neuronal form of  
which comprises 695 amino acids; it has a single  
transmembrane domain (positions 625-648) and a short 47  
10 amino acid cytoplasmic domain (positions 649-695)  
represented in the attached sequence listing under the  
number SEQ ID NO:1.

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elucidated. It is probable that other factors and/or other domains of the molecule are also involved.

For this reason, many studies have tried to establish the physiological and/or physiopathological role of APP and of the various products of its metabolism. In fact, the physiological ligand, if it exists, of the N-terminal domain has not been identified and the signalling pathways are still poorly defined. One of the strategies for making it possible to analyze these signalling pathways is the identification of molecular partners of the cytoplasmic domain.

The cytoplasmic domain of APP, and also various peptides derived from this cytoplasmic domain, have in particular been studied:

- the sequences YTSI, KKKQYTSIHGVEV (SEQ ID NO: 8), GYENPTY (SEQ ID NO: 9) and NPTY have been identified as internalization signals; more precisely, they are considered to be sequences for transcytosis of APP between the basolateral and apical compartments of MDCK epithelial cells (Haass et al., J. Cell Biol., 1995, 128, 4, 537-547; Lai et al., J. Biol. Chem., 1995, 270, 8, 3565-3573; Lai et al., J. Biol. Chem., 1998, 273, 6, 3732-3739);

- the C-terminal cytoplasmic domain (APP-Cter) has been identified as:

- . being involved in regulating the GTPase activity of the  $\alpha$  subunit of heterotrimeric G protein (Brouillet et al., J. Neuroscience, 1999, 19, 5, 1717-1727);

- . interacting with several proteins: Pat-1 interacts with the juxtamembrane domain (KKKQYTSIHG) and with the complete C-terminal domain and is thought to be involved in transporting APP along microtubules, toward the cell surface (Zheng et al., PNAS, 1998, 95, 14745-